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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,959	04/27/1999	MAURIZIO ZANETTI	P-ZA-3519	5037

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/300,959	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/10/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 9/10/04 has been entered. It is noted that the replacement Declaration received also received on 9/10/04 has been entered. Claims 38-68 are currently pending and under examination at this time. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Declaration under 37 CFR 1.1.32

The replacement declaration filed on 9/10/04 is identical to that submitted on 7/29/03, except that the applicant's signature on the replacement declaration is original whereas the one received on 7/29/03 was electronic.

Priority

As noted in previous office actions, claims 38, 41-42, and 44 are entitled to benefit of priority to the filing date of the parent application, April 27, 1998. Claims 39-40, 43, and 45-68 are only entitled to the benefit of priority to the filing date of the instant application, April 27, 1999.

Claim Rejections - 35 USC § 112

The rejection of claims 38, 41, and 42 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below. Please note that the declaratory evidence present in the replacement declaration submitted on 9/10/04 is identical to that of the declaration submitted on 7/29/03 which was fully considered in the previous office action.

Previous office actions identified the following enabled subject matter: methods of stimulating an immune response and methods of treating a condition in a mammal comprising the intrasplenic injection of a DNA plasmid comprising a nucleic acid encoding a heterologous polypeptide antigen operably linked to a B cell expression element, wherein the expression of said heterologous polypeptide antigen in B cells results in the stimulation of an immune response against said antigen.

Applicant's arguments are a reiteration of the arguments submitted on 7/29/03. These arguments were fully considered in the previous office action mailed to applicants on 3/10/04, and were not found persuasive for reasons of record, see pages 4-6 of the 3/10/04 office action. For clarity of prosecution, the relevant sections of the previous office action are provided below.

In regards to routes of immunization other than intrasplenic injection and the unpredictability of targeting B cells in vivo, the applicant argues that the specification identifies other target tissues, such as lymph nodes. However, as previously noted, the cellular composition of the spleen versus gut associated lymph organs, or lymph nodes is very different in terms of the

percentages of different antigen presenting cells and the types of antigen presenting cells present. Although the specification and previously provided declaratory data, exhibit B, demonstrates that direct injection of the spleen results in the generation of immune responses, the specification fails to provide any evidence that the administration of plasmid vectors to any other lymphoid tissue would result in comparable levels of antibody or T cell mediated responses. In the declaration by Maurizio Zanetti, Dr. Zanetti states that there are high percentages of B cells in lymphoid tissues other than spleen. However, it is clear from the percentages provided by Dr. Zanetti that lymph nodes only contain about half the number of B cells as the spleen, and that peripheral blood contains even less. Thus, while the office acknowledges the comments made in the declaration by Maurizio Zanetti, that lymph tissue other than the spleen contains B cells, the declaration fails to provide concrete evidence that the level of B cells in the spleen versus peripheral lymph nodes is equivalent or that the number of B cells present in a peripheral lymph node are capable of stimulating therapeutic immune responses following direct injection of a plasmid or other nucleic acid to the lymph node.

Furthermore, in regards to the post-filing publication provided as exhibit 2 in the declaration filed on 7/29/03, the article by Maloy et al. is not equivalent to the methods of immunization disclosed and claimed by the applicants. While the Maloy et al. reference discloses direct intranodal administration of plasmid DNA encoding an antigen resulting in antigen specific immune responses, the plasmid DNA taught by Maloy et al. does not utilize a B cell specific promoter. Further, Maloy et al. clearly demonstrates that the cells which express the naked DNA vaccine in their experiments are dendritic cells, not B cells (Maloy et al., page 3302-3303, bridging paragraph). Thus, a nexus cannot be made between the results achieved by Maloy

et al. where dendritic cells are transfected following intranodal vaccination and applicants methods which depend on B cell specific expression of the antigen following intranodal injection of the plasmid vector. Therefore, the post-filing evidence of Maloy et al. is not probative for enablement of the instant invention as claimed since the methods used by Maloy result in the expression of the antigen in a different cell population from that claimed by applicants.

In addition, please note that while claim 38 is limited to the administration of the plasmid vector to lymphoid tissue, claims 41-42 are **not** so limited and broadly read on the administration of the plasmid vector by any route of administration. The applicant's instant arguments are directed to the administration to lymphoid tissue and do not address the lack of enablement for administration to non-lymphoid tissue. Instead, the applicant argues that unpredictability is not an issue with respect to the claims and that since the claims recite that the heterologous epitopes are expressed in B cells, any unpredictability for *in vivo* targeting is not applicable. In response, case law teaches (Ex parte Forman, 230 USPQ 546,547 (BPAI 1986)) that "the disclosure of a patent application must enable practice of the invention claimed without undue experimentation", wherein factors involved in the determination of undue experimentation were deemed to include "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or underpredictability of the art and the breadth of the claims." See also MPEP 2164.01(a). Thus, it is clear that unpredictability in the prior art is relevant to whether the claims are enabled by the instant specification. The previous office actions have stated that the specification fails to provide an enabling disclosure for specifically transfecting B cells using any route of

administration. The articles cited in the previous office actions, particularly Deonarian and Miller, clearly teach that specific targeting of a nucleic acid to a particular cell was unpredictable at the time of filing. For example, Deonarain teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al., page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al., page 198, paragraph 2). These references thus establish that at the time of filing, the skilled artisan considered specifically targeting a certain cell population *in* vivo using currently available vector systems unpredictable. The previous office actions further noted that the specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to B cells *in vivo*. The specification as a whole discusses introducing the plasmid into lymphoid tissue and the working examples exemplify intrasplenic injection. The specification does not provide specific guidance or working examples for the targeted expression of a heterologous epitope in B cells by administering plasmid DNA by intramuscular, intradermal, intraperitoneal, or intracerebral injection, or for the number of B cells which must be transfected and express the heterologous epitope in order to stimulate an immune response. As noted above, the spleen contains a large number of B cells, whereas other tissues, including other lymphoid tissues such as lymph nodes or peripheral blood do not. Therefore, in view of the art recognized

unpredictability of targeted gene expression *in vivo*, the lack of guidance provided by the specification for plasmid vectors suitable for specifically targeting B cells, the lack of working examples concerning methods of targeted delivery other than intrasplenic injection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The rejection of claims 38-43, and 58-68 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention, is withdrawn in view of applicant's amendments to the claims.

However, the amendment to claim 39 has resulted in the following new grounds of rejection under 35 U.S.C. 112, second paragraph.

Claim 39 is newly rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as their invention. The applicant has amended claim 39 to recite a method comprising, "administering to a lymphoid tissue ex vivo a plasmid vector nucleic acid molecule comprising a B cell expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, wherein said one or more heterologous epitopes are expressed in a B cell and administering cells expressing said one or more heterologous epitopes to an individual, wherein expression of said one or more heterologous epitopes in said B cell results in stimulation of an immune response". The claim as amended is confusing in that it is unclear what population of cells is administered to the individual. The claim first recites that lymphoid tissue is contacted with the plasmid vector. The claim also recites that B cells, presumably present in the lymphoid tissue express the heterologous epitopes. Finally, the claim recites that it is the expression of the epitopes in those B cells that result in the immune stimulation. However, since the claim recites, "administering cells", it is unclear whether the cells administered are the transfected lymphoid tissue cells as a whole, or only the B cells which were present in the lymphoid tissue. As such, the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 103

Claims 39-40, and 43-68 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,891,432 (1999), hereafter referred to as Hoo, in view of Banerji et al.

(1983) Cell, Vol. 33, 729-740. Please note that the amendments to claim 39 have resulted in the inclusion of this claim in the rejection of record. It is further noted that the previous office action contained a typographical error in the claims listed as rejected. Claim 44 was inadvertently left out of the claims listed as rejected in the previous office action. In view of the correction of the typographical error in this office action, this action has been made **non-final**.

Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that there would have been no motivation to combine the teachings of Hoo et al. with those of Banerji et al. The applicant states that Hoo et al. does not teach using B cell expression elements and that neither Hoo et al. nor Banerji et al. suggest using B cell expression elements in the plasmacytoma cells taught by Hoo et al. In response, the previous office acknowledged that Hoo et al. does not teach using a B cell expression element in plasmids for expression in B cells such as plasmacytoma cells, however, the rejection of record supplements the teachings of Hoo et al. with the teachings of Banerji et al. The rejection of record states that while Hoo et al. generally teaches that the genes encoding the fusion proteins are operatively linked to promoters, and gives the SV40 promoter as an example, Banerji et al. supplements Hoo by teaching a plasmid encoding the b-globin gene operatively linked to the immunoglobulin enhancer which is a B cell specific expression element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Banerji et al. further provides motivation for using a B cell specific expression elements in B cells by teaching that use of the immunoglobulin heavy chain enhancer to express a heterologous gene, b-globin, in B cells results in two fold increase in the magnitude of b-globin expression compared to vectors which utilize the viral SV40 enhancer

(Banerji et al., page 729, abstract, and page 731, column 2, paragraph 3). The previous office action found that based on the increased magnitude of gene expression using the immunoglobulin promoter in B cells versus a viral promoter such as SV40 as taught by Banerji et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the immunoglobulin heavy chain transcriptional elements taught by Banerji et al. for the viral elements taught by Hoo in order to increase antigen expression in B cells such as plasmacytomas. Based on the activity of the immunoglobulin promoter observed by Banerji in B cells and the high degree of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in modifying the plasmid vectors taught by Hoo to include the immunoglobulin promoter and enhancer and using said vectors according to the methods taught by Hoo to generate immune responses.

In response to applicant's arguments that hindsight cannot be used to establish obviousness and that the applicant's disclosure cannot be used to hunt through the prior art for the claimed elements, citing *In re Laskowski* and *Orthopedic Equipement Co. Inc. v. United States*, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The previous paragraph discusses in detail that the motivation for combining the teachings of Banerji et al. with Hoo et al. is found in the teachings of Banerji et al. that an increased magnitude of gene expression can be achieved using an immunoglobulin promoter in B cells

versus using a viral promoter such as SV40. The skilled artisan at the time of filing would have recognized that increased gene expression of an antigen or antigen fusion protein would be desirable in order to enhance immune responses. Thus, the skilled artisan would have been motivated to substitute the immunoglobulin expression elements taught by Banerji et al. for the viral expression elements in the methods of stimulating an immune response taught by Hoo et al.

The applicant further argues that the Hoo et al. reference does not specifically use the words "*ex vivo*" in their specification. Hoo et al., however, clearly teaches methods of stimulating an immune response by administering autologous cells modified *in vitro* to express an antigen or antigen/cytokine fusion protein (see Hoo et al., column 9, lines 25-30 for vaccination with autologous cells) . The term "*ex vivo*" means "outside of the body". Thus, it is clear that Hoo et al. does in fact teach an "*ex vivo*" method when they teach vaccination with transfected autologous cells.

Therefore, for the reasons discussed in detail above, the rejection of record is maintained.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER